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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/915,931	07/26/2001	Hilton A. Salhanick	62694-A/JPW/SHS	8253

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EXAMINER	
DAVIS, DEBORAH A	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 02/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/915,931	SALHANICK ET AL.	
	Examiner	Art Unit	
	Deborah A. Davis	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *136-152 and 155* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *136-152 and 155* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1-26-06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 26, 2006 has been entered. Claims 136-152 and 155 are pending and under consideration.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 136-141 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kuku et al (Journal of endocrinology, 1974, Vol. 62, pages 645-655) in view of Schuurs et al (USP#4,016,043). Kuku et al teaches a double antibody assay for measuring the concentration of TSH (thyroid-stimulating hormone) in urine. Urine samples were taken from subjects with well-defined clinical evidence of hypothyroidism and hyperthyroidism (see summary and introduction). The levels of TSH in the hyperthyroid subjects were lower than those of normal subjects and the level of TSH in hypothyroid subjects were higher. Harsoulis et al teaches the levels of TSH was detected in concentrated normal urine (see introduction) and also **unconcentrated urine (page 647, see Table 1).** Kuku et al teaches that levels in hypothyroid subjects ranged from (25,1 ± 3,3 μu./h, range 10+8-46+5μu./h) and levels in hyperthyroid subjects ranged from (2,6 ± 0,2μu./h, range , 1-3+5) (see page 652). Although TSH concentrations in urine were compared in Tu/h, the levels assayed were taken in ml quantities. A 50ml sample of urine was collected from subjects on thyroxine replacement and was lyophilized and reconstituted in buffer. A .02 ml concentrate of sample was assayed from the original 50ml sample that equaled to a total of 10mls (page 646 paragraphs 1-2). The amount of detectable agent was bound to TSH in urine was determined utilizing a double antibody I-labeled assay (see Recovery Experiments, page 647).

A conversion rate from μu/hr to μu/ml based on the prior art ranges above is the following:

1. (10.8μu/h)(12h) = 129.6μu/10ml =12.96μu/ml - (46.5μu/h)(12h) = 558μu/10ml = 55.8μu/ml. Range = (12.96μu/ml - 55.8μu/ml) = hypothyroidism

2. (1μu/h)(12h) = 12μu/10ml = 1.2ml - (3.5μu/h)(12h) = 558μu/10ml = 55.8μu/ml. Range = (<1.2μu/ml – 55.8μu/ml) = hyperthyroidism

The reference of Kuku et al clearly demonstrated the ability to diagnose hypothyroidism and hyperthyroidism, thus, it appears that the assay of the prior art fall within the ranges of the claimed assay. Although the prior art does not recite the concentrations of TSH and thyroxine in the units described in the claims, the instant invention is deemed to be obvious in the absence of the submission of "WO 80/558" reference conversion table as recited in the instant claim 135, which would demonstrate patentable differences. The office does not have the facilities for examining and comparing applicant's urine concentration ranges with the concentration ranges of TSH of the prior art in order to establish that the ranges of the prior art does not possess the same concentration ranges of the claimed invention. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the concentration ranges of TSH are different than those taught by the prior art and to establish patentable differences. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Kuku et al does not teach the exclusion of radioimmunoassay when measuring TSH in urine.

However, Schuurs et al teaches the disadvantages of using a radioimmunoassay in that although they are sensitive, the requirement of special equipment, trained staff, the need for extra safety measures to protect against and the short half-life span of the radioactive labeling element. The possibility of replacing the radioactive label with an enzyme label is proposed (col. 1, lines 25-42).

It would have been obvious to one of ordinary skill in the art to want to modify the teaching of Kuku to exclude using an radioimmunoassay and replace it with EIA as taught by Schuurs et al for extra safety measures when using radioactive products in a laboratory setting. Further, the exclusion of using radioactive products requires less disposal time, while the Enzyme Immunoassay provides a very simple, and sensitive assay method. With respect to using unconcentrated urine, one skilled in the art would be motivated to do so because it eliminates purification steps wherein the sample can be assayed upon collection, reducing the time required to perform the assay. The use of concentrated and unconcentrated urine constitute obvious variations in parameters which are routinely modified in the art and have not been described as critical to the practice of the invention.

4. Claims 142-152 and 155 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kuku et al, in view of Schuurs and Philo et al (USP#5,108,896).

The teaching of Kuku et al in view of Schuurs et al are set forth above and differ from the instant claims in not teaching dual detection of hormones.

However, Philo et al teaches a dual analyte enzyme immunoassay for assaying two antigens in a single sample wherein reactions occur simultaneously (see abstract). Philo teaches that immunoassays of the present invention are particularly advantageous for assaying pairs of antigens that are found together in physiological samples such as human serum or urine samples. Labels utilized in the instant assay are fluorescein, rhodamine, isothiocyanate and others (col. 7, lines 12-25). Such immunoassays systems are desirable for assaying pairs of hormones including Thyroxine (T4)/ Thyroid Stimulating Hormone (TSH) and others (col. 4, lines 27-36).

It would have been obvious to one of ordinary skill in the art to modify the assay of Kuku et al to include measuring the concentration of Thyroxine (T4) because this hormone is found together with TSH in biological samples such as urine and blood. One skilled in the art would want to measure TSH and Thyroxine in one assay system because if TSH measurements appear discordant with clinical thyroid evaluations, Thyroxine measurements are helpful for identifying inaccurate TSH measurements. Further, dual measurements of TSH/Thyroxine can reduce the time required to run each test separately. With respect to the Thyroxine and TSH measurements of indicated hypothyroidism and hyperthyroidism, it is noted that the prior art has already established that low levels indicates hyperthyroidism while higher are indicative of hypothyroidism. Absent the evidence to the contrary, applicant's claims are directed to the same premise. With respect to using unconcentrated urine, one skilled in the art would be

motivated to do so because it eliminates purification steps wherein the sample can be assayed upon collection, reducing the time required to perform the assay. The use of concentrated and unconcentrated urine constitute obvious variations in parameters which are routinely modified in the art and have not been described as critical to the practice of the invention.

Response to Arguments

5. Applicant's arguments filed January 26, 2006 have been fully considered but they are not persuasive:

6. Applicant's argument that prima facie obviousness does not exist against the instant claimed invention because the cited references in combination, does not teach all elements of the claimed invention, does not have a motive to combine or have a reasonable expectation of success. Applicant contends that the references in combination does not teach unconcentrated urine samples as required by the amended claims. Although the examiner has addressed this limitation in the dependent claims, and in the previous ***Office Action dated August 24, 2005***, applicant maintains that the examiner's assertion is based on hindsight and does not factor in applicant's surprising discovery that measuring the concentration of either urinary TSH or urinary TSH and urinary thyroxine can reliably detect hypothyrodism and hyperthyroidism. This argument is noted but not found to be persuasive.

In response, applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Further, detection of TSH and Thyroxine in urinary samples are taught in the reference of Kuku et al for the detection of hypothyroid and hyperthyroid subjects and are obvious over the instant claimed invention. With respect to the limitation of the urinary samples being unconcentrated, one of ordinary skill in the art would be motivated to use unconcentrated urine because it eliminates purification steps making the sample conveniently ready for use, further Kuku et al also discloses the use of unconcentrated urine samples on page 641, see Table 1).

7. Applicant's argument that Kuku et al and Schuurs et al in combination fail to teach or suggest all elements of the claimed invention or to provide motivation to combine as a reasonable expectation of success. This argument is noted but not found to be persuasive.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention

where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the motivation to combine is found in Schuurs et al (column 1, lines 25-42).

8. Applicant's argument that the examiner's interpretation of Kuku et al TSH concentration ranges are flawed because the invention comprised measuring the concentration in the amount of TSH per unit volume of fluid at a single time point in contrast to Kuku et al that teaches measuring the rate of urinary excretion of TSH in the amount of TSH secreted per unit of time. Applicant maintains that the two measurements are entirely distinct, despite certain quantitative relationships between them, which might exist under certain circumstances. This argument is noted but not found to be persuasive.

In response, applicant points out that the conversion factors are flawed and incorrect but does not point out the flaws. After the conversion factors were complete, the end result of TSH and Thyroxine levels for hypothyroidism and hyperthyroidism measured in microunits per mil as required by applicant's claimed invention. These measurements appear to be to fall with the ranges of the claimed assay. And as stated in the previous Office Action, although the prior art does not recite the concentrations of the TSH and thyroxine in the units described in the claims, the instant invention is deemed to be obvious in the absence of the submission of "WO 80/558" reference

conversion table as recited in the instant claim 136, which would demonstrate patentable differences.

9. Applicant's argument that the reference of Philo et al combined with the references of Schuurs and Kuku et al fail to cure their short comings because the element of an unconcentrated urine sample in the claims as amended is not taught, neither does the reference teach measuring the concentration of urinary TSH or urinary TSH and urinary thyroxine to detect hypothyroidism and hyperthyroidism. This argument is noted but not found to be persuasive for reasons set forth in the above arguments.

Conclusion

10. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah A. Davis whose telephone number is (571) 272-0818. The examiner can normally be reached on 8-5 Monday thru Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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February 17, 2006

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02/17/06